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Pathological factors affecting morbidity in breast cancer with modified radical mastectomy after neoadjuvant therapy

Pathological factors of modified radical mastectomy morbidity

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Abstract

Aim: The aim of this study is to investigate the pathological factors causing postoperative complications in breast cancer patients who underwent modified radical mastectomy (MRM) after neoadjuvant therapy.

Material and Methods: Breast cancer patients who underwent MRM after neoadjuvant therapy in our clinic between 2015 and 2020 were retrospectively included in the study. The relationship between pathological parameters and postoperative complications was evaluated using Mann-Whitney U tests, independent sample t-tests, and chi-square tests and $p<0.05$ was considered significant.

Results: There were 21 patients meeting the study criteria. The mean age of all patients was 48.76±13.98 years (range: 29-88). Morbidity developed in 7 cases (33.3%) and the average length of stay in the hospital was 11.90±4.49 days (range: 6-20). Morbidity increased in patients with advanced age ($p=0.003$) and cases with microcalcification ($p=0.026$) and neural invasion ($p=0.017$) in pathological evaluation, while morbidity decreased in cases with a high mean number of reactive lymph nodes ($p=0.05$). In addition, seroma formation was increased in patients with advanced age and microcalcification. None of the pathological factors affected hematoma formation or surgical site infection.

Discussion: According to the results of our study, we recommend harvesting reactive axillary lymph nodes as much as possible to reduce morbidity. In addition, it should be kept in mind that morbidity may increase in patients with microcalcification and neural invasion in preoperative imaging and at advanced ages.

Keywords

Advanced Age, Microcalcification, Modified Radical Mastectomy, Morbidity, Reactive Lymph Node

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Introduction

Carcinoma of the breast is one of the most common malignancies. In light of the Cancer Statistics 2021 report of Siegel et al., 284,200 new breast cancer cases were expected to be seen in the United States. The same report also predicted that approximately 44,130 people would die due to breast cancer in the United States [1]. The treatment of breast cancer is managed with multidisciplinary approaches. These approaches include surgery, radiotherapy, chemotherapy, hormone therapy, immunotherapy, and their combinations.

Preoperative tumor staging is the most important factor in deciding on treatment. Diagnostic imaging work-up and mass biopsy play important roles in establishing a diagnosis and informing surgical decisions on the management of the primary tumor, staging of the axilla, and the sequence of therapy [2]. Once a diagnosis of breast cancer is established, the extent of disease is assessed, which, for the most part, determines whether or not preoperative (neoadjuvant) systemic therapy is indicated. For advanced-stage tumors, systemic therapy, also known as neoadjuvant treatment, is administered as the initial treatment to reduce tumor volume and will render approximately 80% of patients operable [3]. Based on the evaluation after neoadjuvant treatment, modified radical mastectomy (MRM) is one of the surgical options.

Seroma, hematoma, wound infection, flap necrosis, pain, and edema of the hand are the main complications of MRM. Post-mastectomy complication rates are variable. In the study of Browne et al., the overall complication rate was 10.1% for patients undergoing mastectomy without reconstruction [4]. On the other hand, in the study by Berry et al., the total complication rate after mastectomy was 32.5% [5].

The aim of this study is to investigate the possible pathological factors increasing postoperative complications in breast cancer patients who underwent MRM after neoadjuvant therapy.

Material and Methods

Patients undergoing MRM for breast cancer after neoadjuvant therapy between 2015 and 2020 at Erzurum Regional Education and Research Hospital, Erzurum, Turkey were included in the study. Patients who were diagnosed and treated at external centers before admission to our center and patients who underwent bilateral MRM were excluded from the study.

Patients' hospital records, consultation and operation notes, pathology reports, and clinical charts were used. Each patient's demographical data (gender, age), tumor localization, pathology reports, and postoperative complications were examined. In pathology reports, hormone receptor status, lymphatic and vascular invasion status, presence of microcalcification, presence of axillary lymph nodes (reactive, metastatic, total), and lymph node ratio were investigated. The TNM stage was defined according to the American Joint Committee on Cancer (Version 8) guidelines for breast cancer. The relationships between pathological parameters and postoperative complications and their subgroups were evaluated.

Statistical Analysis

Statistical evaluations were carried out using SPSS 22.0 (IBM Corp., Armonk, NY, USA). The normality distributions of quantitative variables were checked using the Shapiro-Wilk test. Either an independent t-test or Mann-Whitney U test was used according to the results of the Shapiro-Wilk test. The chi-square test was used to compare qualitative variables. Differences with p-values below 0.05 were considered statistically significant.

Ethical approval was obtained from the Noninvasive Clinical Research Ethics Committee of Erzurum Regional Education and Research Hospital, Erzurum, Turkey (Decision Number: 2021/12-206).

Results

There were 21 patients meeting the study criteria. The mean age of all patients was 48.76±13.98 years (range: 29-88). Thirteen (61.9%) had a tumor located in the left breast. Complications in the first 30 days after surgery were defined as morbidity. Morbidity developed in 7 patients (33.3%) (seroma in 5 patients, hematoma in the axillary region in 1 patient, and wound infection in 1 patient), and the average length of stay in the hospital was 11.90±4.49 days (range: 6-20).

In the pathological examination of the patients, the mean tumor diameter was 31.23±13.04 mm (range: 10-65). The most common pathological T stage was T2 at 81%, while the most

Table 1. Clinicopathological parameters of the patients

Parameters	Value or n (%)
Age (years)	48.76±13.98 (29-88)
Pathological evaluation	
Tumor location	
· Right breast	8 (38.1%)
· Left breast	13 (61.9%)
Tumor diameter (mm)	31.23±13.04 (10-65)
Lymph node parameters	
· Number of reactive lymph nodes	15.14±8.35 (3-38)
· Number of metastatic lymph nodes	2.85±3.53 (0-12)
· Number of total lymph nodes	18±7.23 (6-38)
· LNR	0.17±0.22 (0-0.7)
Pathological T stage	
· pT1	1 (4.8%)
· pT2	17 (81%)
· pT3	3 (9.5%)
· pT4	1 (4.8%)
Pathological N stage	
· pN0	10 (47.6%)
· pN1	4 (19%)
· pN2	7 (33.3%)
M stage	
· M0	15 (71.4%)
· M1	6 (28.6%)
Microcalcification positivity	3 (14.3%)
Lymphovascular invasion positivity	9 (42.9%)
Neural invasion	7 (33.3%)
Receptor positivity	
· Estrogen receptor	18 (85.7%)
· Progesterone receptor	18 (85.7%)
· HER2 receptor	10 (47.6%)
· p53	3 (14.3%)
Overall morbidity	7 (33.3%)
Length of hospital stay (mean, days)	11.90±4.49 (6-20)

LNR: Lymph node ratio, T: tumor, N: node, M: metastasis.

common pathological N stage was N0 at 47.6%. On the other hand, in the evaluation of patients with advanced imaging tools, 6 patients had distant metastasis (M1 stage). There were axillary metastatic lymph nodes in 11 cases (52.4%) with a mean diameter of 2.85±3.53 mm (range: 0-12). The pathological data of the patients are shown in Table 1.

Morbidity increased in patients with advanced age (p=0.003) and those with microcalcification (p=0.026) and neural invasion (p=0.017) in pathological evaluation, while morbidity decreased in cases of a high mean number of reactive lymph nodes (p=0.05). In addition, postoperative seroma after MRM affected advanced age (p=0.019) and presence of microcalcification

Table 2. Comparison of the patients according to presence of morbidity

Variables	Morbidity positive n=7	Morbidity negative n=14	p
Age (mean)	60.71	42.78	0.003*
Pathological evaluation			
Tumor location			
· Right breast	2 (25%)	6 (75%)	0.656**
· Left breast	5 (38.5%)	8 (61.5%)	
Tumor diameter (mm)	35.14	29.28	0.345*
Lymph node parameters			
· Reactive lymph nodes (mean rank)	7	13	0.05***
· Metastatic lymph nodes (mean rank)	12.71	10.14	0.400***
· Total lymph nodes (mean)	14.57	19.71	0.128*
· LNR (mean rank)	12.79	10.11	0.360***
Pathological T stage			
· pT1	0 (0%)	1 (100%)	0.199****
· pT2	6 (35.3%)	11 (64.7%)	
· pT3	0 (0%)	2 (100%)	
· pT4	1 (100%)	0 (0%)	
Pathological N stage			
· pN0	3 (30%)	7 (70%)	0.743****
· pN1	2 (50%)	2 (50%)	
· pN2	2 (28.6%)	5 (71.4%)	
M stage			
· M0	5 (33.3%)	10 (66.7%)	>0.999**
· M1	2 (33.3%)	4 (66.7%)	
Microcalcification			
· Yes	4 (22.2%)	14 (77.8%)	0.026**
· No	3 (100%)	0 (0%)	
Lymphovascular invasion			
· Yes	3 (33.3%)	6 (66.7%)	>0.999**
· No	4 (33.3%)	8 (66.7%)	
Neural invasion			
· Yes	5 (71.4%)	2 (28.6%)	0.017**
· No	2 (14.3%)	12 (85.7%)	
Receptor positivity			
· Estrogen receptor			
o Yes	7 (38.9%)	11 (61.1%)	0.521**
o No	0 (0%)	3 (100%)	
· Progesterone receptor			
o Yes	7 (38.9%)	11 (61.1%)	0.521**
o No	0 (0%)	3 (100%)	
· HER2 receptor			
o Yes	3 (30%)	7 (70%)	>0.999**
o No	4 (36.4%)	7 (63.6%)	
· p53			
o Yes	1 (33.3%)	2 (66.7%)	>0.999**
o No	6 (33.3%)	12 (66.7%)	
LOS (mean, days)	9.79	11.61	0.535***

LNR: Lymph node ratio, T: tumor, N: node, M: metastasis, LOS: length of stay.
*Independent t-test, **chi-square test, ***Mann-Whitney U test, ****likelihood ratio test.

Table 3. Comparison of the patients according to presence of seroma

Variables	Seroma positive n=5	Seroma negative n=16	p
Age (mean rank)	16.60	9.25	0.019*
Pathological Evaluation			
Tumor location			
· Right	1 (12.5%)	7 (87.5%)	0.606**
· Left	4 (30.8%)	9 (69.2%)	
Tumor diameter (Mean rank)	14.80	9.81	0.130*
Lymph node parameters			
· Reactive (Mean rank)	7.20	12.19	0.130*
· Metastatic (mean rank)	12.50	10.53	0.548*
· Total (mean rank)	7.50	12.09	0.153*
· LNR (mean rank)	12.80	10.44	0.495*
Pathological T stage			
· pT1	0 (0%)	1 (100%)	0.212***
· pT2	4 (23.5%)	13 (76.5%)	
· pT3	0 (0%)	2 (100%)	
· pT4	1 (100%)	0 (0%)	
Pathological N stage			
· pN0	2 (20%)	8 (80%)	0.415***
· pN1	2 (50%)	2 (50%)	
· pN2	1 (14.3%)	6 (85.7%)	
M stage			
· M0	3 (20%)	12 (80%)	0.598**
· M1	2 (33.3%)	4 (66.7%)	
Micro calcification			
· Yes	3 (100%)	0 (0%)	0.008**
· No	2 (11.1%)	16 (88.9%)	
Lympho-vascular invasion			
· Yes	2 (22.2%)	7 (77.8%)	>0.999**
· No	3 (25%)	9 (75%)	
Neural invasion			
· Yes	3 (42.9%)	4 (57.1%)	0.280**
· No	2 (14.3%)	12 (85.7%)	
Receptor positivity			
· Estrogen receptor			
o Yes	5 (27.8%)	13 (72.2%)	0.549**
o No	0 (0%)	3 (10%)	
· Progesterone receptor			
o Yes	5 (27.8%)	13 (72.2%)	0.549**
o No	0 (0%)	3 (10%)	
· HER2 receptor			
o Yes	2 (20%)	8 (80%)	>0.999**
o No	3 (27.3%)	8 (72.7%)	
· p53			
o Yes	5 (27.8%)	13 (72.2%)	0.549**
o No	0 (0%)	3 (10%)	
LOS (mean, days)	9.70	11.41	0.603*

LNR: Lymph Node Ratio, T: Tumor, N:node, M: Metastasis.
*Mann Whitney U test, ** Chi-square test, ***Likelihood Ratio test.

in the pathology specimen. Neither postoperative hematoma nor surgical site infection was affected by the parameters investigated. The comparison of the patients according to the presence of morbidity is shown in Table 2 and the comparison according to seroma is shown in Table 3.

Discussion

Breast cancer is a global health problem all over the world. In suitable cases, the main treatment is mastectomy with or without axillary lymph node dissection. However, for advanced-stage diseases, the first step of treatment is chemotherapy. After the chemotherapy process, patients are mostly scheduled for MRM [6].

The rate of postoperative complications after mastectomy ranges widely from 8% to 26% [7]. The most common complications following MRM are seroma, lymphedema, infection, and wound necrosis [8]. Postoperative complications cause a prolonged hospital stay and add psychological and economic burdens for the patient. Therefore, it is important to know the factors that prevent complications. In this study, we have evaluated morbidity in a different way, aiming to show the pathological factors that prevent morbidity.

Seroma is one of the most common complications after mastectomy with an incidence of 3% to 85% [9]. The seroma prevalence in this study was 23.8%. Some authors believe that seroma occurs due to acute inflammatory exudates in response to surgical trauma and the acute phase of wound healing [10]. During dissection, some lymph pathways are opened and lymph fluid leaks out. The leaking lymph fluid accumulates in the spaces where the adhesion of the skin flaps is difficult, especially in the axilla. Generally, seroma accumulates in the first 2 weeks postoperatively and then begins to resorb after being stable in the next 2-3 weeks. The controllable predictive factors for seroma formation are still unknown. Although the results are inconsistent, some factors affecting seroma formation have been reported. Can-Özkan et al. showed in their study that no statistical correlation was found between age, tumor diameter, or number of lymph nodes removed and seroma development [11]. However, in this study, seroma after mastectomy was mostly seen at older ages and the prevalence of seroma was in keeping with the literature range.

The roles of preoperative factors like age, obesity, and hypertension in seroma formation were studied with conflicting results. In the study of Garzali and El-Yakub, patients with higher body mass index had higher risk of seroma [12]. Intraoperative factors studied include the extent of dissection and the choice of dissector. Extensive axillary dissection and the use of electrocautery for dissection have been found to be significant in the development of seroma. Postoperative factors like short duration of drainage less than 10 days and early shoulder exercise have been associated with postmastectomy seroma. On the other hand, Pan et al. showed that neither tumor diameter nor presence of axillary lymph node metastasis affected postoperative seroma, as was seen in our study [13]. Suresh et al. showed that patients older than 40 years, those with tumor sizes above 30 mm, patients with more than 5 metastatic lymph nodes harvested, and those with total lymph node count above 20 had a higher probability of seroma in their study [14]. Petrek et al. found that the number and extent of axillary lymph node involvement were the most significant factors in the causation of seroma [15]. Unlike previous studies, neither tumor size nor lymph node parameters were seen to affect seroma formation in the present report. In contrast to other studies in the English-language literature, we found that the presence of microcalcification in pathological specimens was a poor prognosis factor for seroma development after mastectomy.

Hematoma after mastectomy occurs in 2% to 10% of all mastectomy cases. Our study's hematoma rate was 4.76%. The widespread use of electronic devices has reduced the incidence of hematoma formation [16]. Seth et al. found that age difference, tumor size, tumor localization, and lymph node number had no effects on postoperative hematoma, as did the present study.

Breast surgeries are considered essentially clean surgeries and do not require antibiotic treatment. Incidence rates for postoperative wound infections are variable and range from 3% to 19% [17]. Our study's surgical site infection rate was 4.76%. Predisposing factors for infection include seroma, separation in the wound, thin skin flaps that may have limited nutrition, impaired lymphatic drainage around the axilla, advanced age, diabetes, malnutrition, and possible host defense mechanisms [18-20]. In the study conducted by Nieto et el., patients with advanced age had a higher rate of surgical site infections [21]. However, age was not a factor affecting the surgical site infection rate in our sample.

Conclusion

Complications after mastectomy are problems that every surgeon may encounter. As in our study, seroma is the most common morbidity following mastectomy. Advanced age is a poor prognosis factor for both overall morbidity and seroma formation. The presence of neural invasion and microcalcification had negative effects on overall morbidity, while the presence of microcalcification alone had a negative effect on seroma formation. However, the number of reactive lymph nodes harvested showed a protective effect on morbidity. None of the pathological factors affected hematoma formation or surgical site infection. To date, there has not been a study evaluating the relationship between pathological factors and morbidity and morbidity subgroups, and further studies with larger numbers of cases are needed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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